REMARKS

Claim 1 has been amended to place the Markush grouping in proper format. Claim 3 has been amended for purposes of precision.

Applicants respectfully submit that claims 1-9 are not obvious under 35 USC §103(a) over Nagafuzi et al. (US 5,290,569) either alone, or in view of Klimesh et al. (US 4,880,585). To establish *prima facie* obviousness, some suggestion or motivation to modify the references must be shown from the references themselves, or from the knowledge generally held by those of skill in the art. *In re Fine*, 958 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). No such suggestion or motivation, in light of the following additional remarks, has been set forward. Further, the Nagafuzi reference teaches away from the presently claimed invention, and modification in the manner presently claimed would make the subject invention therein unsatisfactory for its intended purpose. Such a situation argues against a finding of *prima facie* obviousness. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

The presently claimed invention is drawn to

> A process for producing *solid dosage forms* ... wherein [various substituents] are mixed and plasticized [under certain conditions] and the *resulting plastic mixture is shaped to produce the dosage form.*

(claim 1, emphasis supplied). Contrastingly, Nagafuzi discloses

> A process for preparing a *coated* composition ... which comprises centrifugally *granulating* a mixture [of an] active substance and a first thermomelting material ... and *coating the resultant granules* with a second thermomelting material ... .

(abstract, col.1:37-44). The most readily apparent difference between the present

claims and the disclosure of Nagafuzi is in the final form the mixed material takes.

In Nagafuzi, an active material is combined with a first thermomelting binder (col.3:64-68) and other excipients, if desired (col.3:23-35), in a centrifuged force granulating procedure (col.3:58-61), following which "the grown granules are cooled to give hard and compact particles" (col.4:45-46). These granules are then coated with a second thermomelting material, "using a mixer of the same kind as employed in the granulating step" (col.4:47-52). The Nagafuzi process ultimately results in "coated granules having hard and compact coating layers at the surfaces" (col.5:13-14).

In contrast, the presently claimed invention combines the relevant ingredients and plasticizes them together, with the plasticized mixture then shaped into dosage forms (claim 1). Though Nagafuzi indicates that granular preparations may be compressed to form tablets (col.1:22-25), such a granular preparation is not equivalent to a plasticized mixture of the relevant ingredients. As Nagafuzi indicates that uncoated granules "may afford an unpleasant taste," and that "such non-coating makes it difficult to control the site or time at which the pharmaceutically active substance exerts its pharmaceutical efficacy" (col.1:25-30), tabletting a non-coated, plasticized mixture of the ingredients would defeat two key purposes of the Nagafuzi invention.

Ending the Nagafuzi process at the point indicated in Example 1 therein would produce an unsatisfactory granular product, and proceeding through the steps disclosed in Example 3 would produce a *coated* granular product. Neither of these is, or suggests, the plasticized mixture of the present claims, and the closest of the two (example 1) defeats the purpose of protecting from the unpleasant taste. Additionally,

the object of Nagafuzi's coating, with regard to control of site and timing of active ingredient release, is to *prolong* the time it takes for an individual granule to dissolve (col.1:27-30, col.2:27-30, col.10:60-65, test examples 1-3, claim 2). Contrastingly, the present invention aims to *shorten* the active ingredient release time (specification p.2:37-39, pp.19-21). Modification of Nagafuzi in the manner indicated by the present invention would make that invention unsatisfactory for its stated intention, and one of skill in the art would not be motivated by Nagafuzi to attempt to *shorten* the active ingredient release time.

Shortening of the active ingredient release time is achieved at least in part by including cyclodextrin in the presently claimed invention. Example 1 of the specification shows 48% release after 10 minutes, whereas comparative example 1 shows 8% release after the same time period (pp.19-20). Similar results are found in example 2 and comparative example 3. Nagafuzi includes cyclodextrin in the granules *to be coated*, but does not indicate any particular role that this cyclodextrin plays in the composition. Accordingly, no statement of motivation can be said to have been set forward from the references or the knowledge generally held by those of skill in the art.

The Klimesh reference does nothing to remedy this deficiency. Accordingly, applicants respectfully request that the rejection of claims 1-9 under 35 USC §103(a) as obvious over Nagafuzi, alone or in view of Klimesh, be withdrawn.

Applicants further submit that claims 1-9 are not obvious under 35 USC §103(a) over Baert et al. (WO 97/18839). Again, to establish *prima facie* obviousness, some suggestion or motivation to modify the references must be shown from the references

themselves, or from the knowledge generally held by those of skill in the art. *In re Fine*, 958 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). No such suggestion or motivation, in light of the following additional remarks, has been set forward. Further, the Baert reference also teaches away from the presently claimed invention, a situation that argues against a finding of *prima facie* obviousness. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Baert discloses a process for creating a cyclodextrin/active ingredient solid mixture through melt-extrusion of the ingredients in an extruder (p.4:13-22). The extrudate is "milled to obtain a powdered form of the mixture" (p.7:5-6) or after cooling, "is fed into a chopper which forms pellets[, which themselves] may be further milled" (p.7:22-23). Though plasticizers are mentioned as optional ingredients in the melt-process (p.6:1-5) none of the "conventional pharmacollogically acceptable plasticizers" listed (p.6:1) or known (see attached Ullmann's article on Plasticizers) is or can be considered a "polymeric binder ... having a molecular weight above 1000" (present claim 1; each of the plasticizers listed have molecular weights well below 1000). In Example 5 of Baert, it is the formed, cooled and milled extrudate that is then combined with the crospovidone (apparently in powder form) and tabletted.

This differs from the present invention in several ways. In the melt-extrusion process, for instance, inclusion of a polymeric binder is not mentioned. The addition of crospovidone to the milled extrudate prior to tabletting is not the same, nor suggestive of, addition of a polymeric binder to the melt process itself. Baert teaches away from including a liquified polymeric binder, by stating that

> It will be appreciated by a person skilled in the art that mixing two or more solids, i.e. one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

(p.6:15-19). Those of skill in the art would likewise expect a different product when the process is carried out in the presence of a liquified polymeric binder. Accordingly, modification of Baert's disclosure to include a polymeric binder would not produce the product contemplated therein. This would defeat the purposes contemplated by Baert.

Further, Baert emphasizes the importance of the inside temperature of the extruder, and all exemplifications of the process are carried out at temperatures ranging from 239°C to 292°C (Tables 1 and 2, pp.12-13). This teaching would not lead one of skill in the art to modify the Baert process to lower the temperature below 220°C, as is required by the presently claimed invention. Rather, this would lead one of skill in the art *away* from the presently claimed invention, as such temperatures appear to be necessary to achieve the Baert reference's desired effect.

As Baert does not teach or suggest elements of the presently claimed invention, but teaches away from the suggested modifications, applicants respectfully submit that claims 1-9 are not obvious over this reference. Accordingly, withdrawal of the rejection under 35 USC §103(a) based on Baert is requested.

In view of the foregoing amendments and remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

Please charge any shortage in fees due in connection with the filing of this

paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claims 1 and 3 to read as follows:

1. (amended) A process for producing solid dosage forms which are suitable for oral or rectal administration for humans and animals, wherein

a) 0.5 to 30% by weight of at least one active ingredient,

b) 0.5 to 70% by weight of at least one cyclodextrin,

c) 10 to 98% by weight of at least one polymeric binder, selected from the group consisting of polyethylene glycol having a molecular weight above 1000, polyvinylpyrrolidone, and [or] copolymers comprising N-vinylpyrrolidone and vinyl acetate, and

d) 0 to 50% by weight of conventional excipients[.]

are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to produce the dosage form.

3. (twice amended) A process as claimed in claim 1, wherein the plastic mixture is shaped in a molding calendar to produce the dosage forms.

COPY OF ALL CLAIMS

1. (amended) A process for producing solid dosage forms which are suitable for oral or rectal administration for humans and animals, wherein

   a) 0.5 to 30% by weight of at least one active ingredient,

   b) 0.5 to 70% by weight of at least one cyclodextrin,

   c) 10 to 98% by weight of at least one polymeric binder, selected from the group consisting of polyethylene glycol having a molecular weight above 1000, polyvinylpyrrolidone, and copolymers comprising N-vinylpyrrolidone and vinyl acetate, and

   d) 0 to 50% by weight of conventional excipients

   are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to produce the dosage form.

2. A process as claimed in claim 1, wherein the molar ratio between active ingredient and cyclodextrin is in the range from 0.1 to 4.0.

3. (twice amended) A process as claimed in claim 1, wherein the plastic mixture is shaped in a molding calendar to produce the dosage forms.

4. A process as claimed in claim 3, wherein a molding calender with counterrotating molding rolls is used, with at least one of the molding rolls having on its surface depressions to receive and shape the plastic mixture.

5. A solid dosage form which is essentially free of aliphatic C_2-C_8-di- and -tricarboxylic acids and aromatic C_6-C_{10}-monocarboxylic acids, obtainable by a process as claimed in claim 1.

6. A solid dosage form as claimed in claim 5, wherein at least 10% by weight of the active ingredient are present in the form of a cyclodextrin/active ingredient complex.